Fish scale development: **Hair today, teeth and scales yesterday?**

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A group of genes in the tumour necrosis factor signalling pathway are mutated in humans and mice with ectodermal dysplasias – a failure of hair and tooth development. A mutation has now been identified in one of these genes, *ectodysplasin-A receptor*, in the teleost fish *Medaka*, that results in a failure of scale formation.

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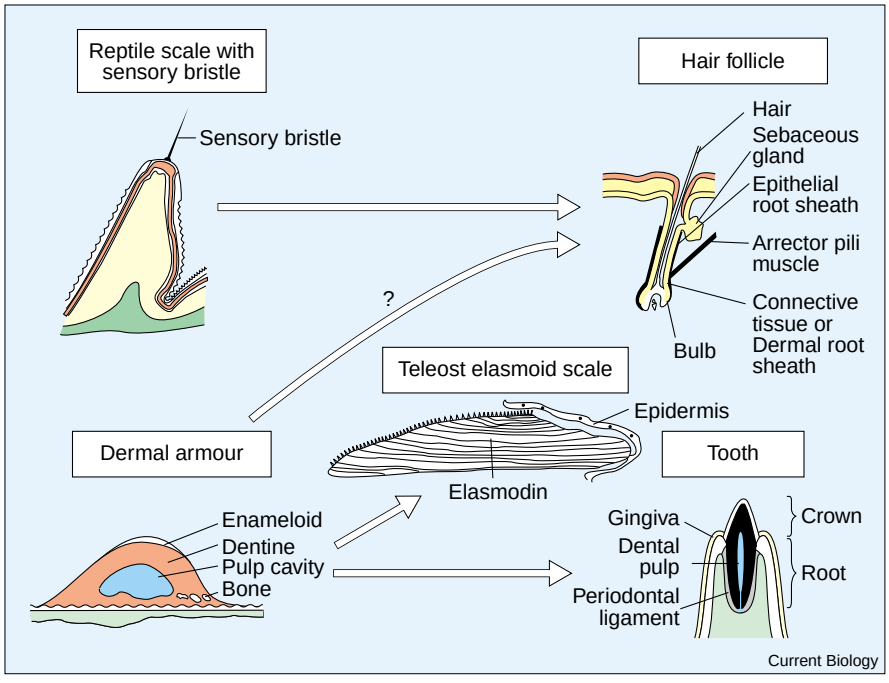
Inferring homology for organs is an essential prerequisite for understanding evolution. Comparison of organ morphology along with the knowledge of the evolutionary origin remains the principal way of identifying homologies and whereas comparison of gene expression during organ development can also be useful, the promiscuity of genetic pathways often makes this less informative. In some instances however molecular homologies can reveal some surprises about development and evolution.

At first glance, hair, teeth and scales appear to have little in common aside from all being vertebrate appendages (see Figure 1). Hair and fish scales are distributed over the body surface in an orderly pattern, but are morphologically, and evolutionary different. Teeth and fish scales are morphologically different too, but both are elements of the dermal skeleton and they are supposed to be derived from a common ancestor [1]. Morphologically and evolutionarily, teeth and hair are also very different but both share a number of common developmental pathways, such as the Hedgehog, Bone morphogenetic protein and Wnt signalling pathways, reflecting the similarities of their early development involving epithelial–mesenchymal interactions [2]. A recent paper published by Kondo and colleagues [3] in *Current Biology* now provides the first evidence for a genetic pathway that is essential for the formation of both fish scales and hair and which is also required for normal tooth development.

The story begins, appropriately enough, with Charles Darwin who in 1875 related the story of the 'toothless men of Sind' whose absence or abnormality of teeth and body hair was caused by the genetic condition of hypohydrotic ectodermal dysplasia [4]. This condition also includes abnormal or absent teeth and mucous glands. The mutated gene responsible for this condition was identified in 1994 and found to code for a transmembrane protein, ectodysplasin or EDA, with similarity to tumour necrosis factor (TNF) family members [5]. A spontaneous mouse mutant,

Figure 1

Basic structure and possible evolutionary relationship between vertebrate ectodermal/dermal appendages. Hair follicles are ectodermally derived and are believed to have evolved from reptile scales. Teeth and teleost scales are dermally derived and may have evolved from a common ancestor, the dermal armour of ancient fishes. The EDA/EDAR cell–cell signalling interaction is required for the development of hair, scales and teeth.



Tabby, develops only one of the four types of mouse hair and has tooth defects and the *Tabby* gene was found to be homologous to human EDA [6–8]. *Downless*, another spontaneous mouse mutant with an identical phenotype to *Tabby*, was found to encode a TNF-like receptor, EDAR that interacts with EDA, indicating a role for these molecules in cell–cell interactions [9,10]. Mutations in EDAR have also been identified in human ectodermal dysplasia. TNF signalling via EDA–EDAR interactions is thus essential for normal hair follicle and tooth development. This molecular link between hair and tooth development has been assumed to be related to the commonality of early development involving epithelial–mesenchymal interactions.

Teleosts are covered with elasmoid scales — appendages that develop from a dermal mesenchyme [1]. The *rs-3* mutant in the teleost *Medaka* results in a failure of the development of most scales. The *rs-3* locus has now been shown to encode EDAR and thus mammalian hair loss and failure of fish scale development involve the same TNF pathway [3]. Although they are both skin appendages, hair and scales are not homologous organs. Hair, and also feathers, are ectodermal structures containing keratin that probably evolved from keratinised epidermal scales in a common ancestor of mammals and reptiles. Fish scales on the other hand do not contain keratin. They are mineralised dermal elements that possibly contain dentine- and enamel-derived proteins.

The identification of a common requirement for development for hair and fish scales thus reflects a common developmental mechanism for appendage formation involving epidermal–dermal interactions and probably not a direct evolutionary link. The EDA/EDAR TNF signalling pathway is thus used during the development of evolutionarily unrelated skin appendages and therefore has similarities with the function of Pax6 in vertebrate and invertebrate eye development where a common genetic pathway is used for development of functionally similar but morphologically unrelated organs [11].

The evolutionary link between fish scales and teeth is more substantial. Scales in teleost fish evolved from the dermal armour covering the body of ancient vertebrates. The structural and developmental similarities of fish dermal armour and mammalian teeth has led to the suggestion that teeth evolved by internalisation of dentin-containing dermal armour 'odontodes' into the oral cavity. Although this hypothesis has been challenged, the common role for TNF signalling in scale and tooth development is consistent with the idea that teeth evolved from fish dermal armour. The story is however far from complete as *Medaka rs-3* mutants have normal teeth (Kondo S, personal communication). Other *Medaka* mutants are known that have scale defects and it will be interesting to see if these involve components of the TNF pathway, such as EDA, or if they are homologues of a number of as yet uncloned loci in the mouse, such as *crinkled*, mutants of which have defective tooth and hair development [12].

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